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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,014	11/22/2000	Kyriacos A. Mitraphanous	550 184	4760

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EXAMINER	
GUZO, DAVID	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/701,014	MITRAPHANOUS ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 November 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ *Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application)* since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ *The translation of the foreign language provisional application has been received.*

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/20/03 has been entered.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27 and 31 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained for reasons of record in the previous Office Action (Mailed 3/20/03) and for reasons outlined below. Claim 27 is added to this rejection because the only disclosed use for a retroviral vector system comprising a nucleic acid sequence having a therapeutic effect or encoding a protein which has a therapeutic effect is for gene therapy.

Applicants traverse this rejection by providing a Declaration under 37 CFR 1.132 by Drs. Wong and Mazarakis (both employed by the assignee) which allegedly demonstrates that the claimed vector system can be employed in a therapeutic context. Applicants and declarant assert that the instant vector system can protect neuronal cells from degeneration and cellular loss in a rat stroke model. Applicants indicate that since the rat stroke model is art recognized as correlating with a specific condition, i.e. stroke, said model is acceptable as a working example. Applicants assert that when testing a vector for gene delivery, a good experimental model should test whether the gene of interest is introduced into the target cells and whether the genetic phenotype of the cell is altered. Applicants assert that the data presented in the declaration using the rat stroke model clearly pass this test as neuronal protection is demonstrated in transduced cells.

Applicant's arguments filed 8/20/03 have been fully considered but they are not persuasive. With regard to the 1.132 Declaration, said declaration is not sufficient to overcome the outstanding 35 USC 112, 1st paragraph rejection. First, the Declaration recites use of pseudotyped retroviral vectors which are not disclosed in the instant specification. Specifically, declarants recite use of the pONYX8Zrabies vector; this vector is not disclosed in the instant specification and its' characteristics are unknown. Second, the declaration recites use of the pONYX8Zrabies vector to express the anti-apoptotic molecule Bcl2. The instant specification does not teach use of this molecule to protect neurons from glutamate induced cell damage or death. Since the vector used by declarants is not disclosed in the instant specification, it is unclear what properties it

possesses and whether said undisclosed properties are responsible for its' ability to transduce rat neuronal cells and protect said cells from damage in a rat stroke model. Data derived from the use of vectors not disclosed in the instant specification cannot be used to provide convincing evidence of the enablement of the instantly recited vector system.

Third, neither declarants nor applicants have provided evidence that the rat stroke model used in the declaration is art recognized as being predictive of results which the skilled artisan would expect to see **in gene therapy treatments of humans** using the recited rabies G protein pseudotyped vector system. An animal model must be evaluated in regard to what potential therapy is being tested in the model. In the instant case, the therapy involves gene therapy using a pseudotyped retroviral (lentiviral) vector to deliver therapeutic genes to neuronal cells. As noted by applicants, a suitable animal model should be one where the disease condition is art recognized as being correlated to the same disease condition in humans. However, common sense dictates that the nature of the therapy being tested in the animal model must also be considered and whether the results of the therapy in the animal model are such that the skilled artisan would expect to observe the same results in patients. In the gene therapy art, the prior art is replete with successful animal model data which has not translated into successful human clinical results. Indeed, Juengst (BMJ, June 28, 2003, Vol. 326, pp. 1410-1411) notes that since 1990, many bench research studies and animal studies have resulted in over 1000 clinical trials but without much clinical success and only one example of a "cure" using retroviral vectors. However, the one

example of a "cure" resulted in insertional mutagenesis in patients and development of T-cell acute lymphoblastic leukemia. For the above reasons and for reasons of record, the 35 USC 112, 1st paragraph (enablement) rejection is maintained.

Claims 32-33 and 40 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of selectively delivering nucleotide sequences to (or transducing) neuronal cells *in vitro*, does not reasonably provide enablement for said method *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and the invention commensurate in scope with these claims.

The grounds for this rejection are the same as indicated in the above enablement rejection of claim 31 since the only disclosed use for the claimed method *in vivo* is for gene therapy.

Claims 21-33 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants claim a retroviral delivery system comprising retroviral vectors pseudotyped with a "derivative" of the rabies G protein, pharmaceutical compositions comprising said retroviral delivery system and methods of selectively delivering genes

of interest to neuronal target cells. The claims read on a genus of retroviral vectors comprising derivatives of the rabies G protein. The specification (and prior art) provide a written description of the rabies G protein and numerous mutants and variants of said protein.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus. In the instant case, the genus encompassed by the instant claims reads on any molecule that can be derived, by any process, from any naturally occurring rabies G protein, or alternatively the molecule can be chemically synthesized, etc. The relationship between the rabies G protein and the derivative appears to be that the derivative be able to pseudotype a retroviral vector particle so that it can selectively transduce neuronal cells at a higher efficiency than retroviral vectors pseudotyped with the VSV G protein. The claims read on molecules that can function to selectively transduce neuronal cells without necessarily having any structural relationship with the rabies G protein (other than, for example, retention of one or more amino acid residues found in the rabies G protein). Therefore, the structure-function relationship between the rabies G protein and the derivative is not established because the derivative need not comprise any region of the rabies G protein molecule. Since the claims recite the

claimed derivatives by function only without a disclosed correlation between the structure of the rabies G protein derivatives and their function, given that the claimed genus reads on any molecules capable of facilitating retroviral transduction of neuronal cells (these would be expected to vary greatly and would include any molecules that could bind to any of the cellular receptors specific for neuronal cells), and given that the sequence of the rabies G protein need not be conserved, it must be considered that the skilled artisan would not conclude that applicants were in possession of the claimed genus. It must be considered that the examples disclosed by applicants and the prior art would not be a representative number of species sufficient to convince the skilled artisan that applicants were in possession of the claimed genus of derivatives.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21, 34-39 (and dependent claims) are vague in the recitation of a retroviral vector delivery system capable of "selectively transducing human target cells with higher transduction efficiencies in neuronal cells". It is unclear if applicants are claiming a vector system capable of selectively transducing **all human target cells** but with higher efficiencies in neuronal cells or a vector system which selectively transduces

human neuronal cells or a vector system which selectively transduces any human target cells and **any neuronal cells from any species**, etc.

Claims 21-33 and 40 are vague in the recitation of a "derivative" of the rabies G protein. It is unclear how closely related to the rabies G protein starting material the derivative needs to be in order to be defined as a "derivative". Also, since the mechanisms whereby the derivative is obtained are not defined by applicants, the metes and bounds of the resultant claimed subject matter are unclear.

Claims 23-24 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 23-24 depend from claim 21. Claim 21 recites a retroviral vector system having a rabies G protein coding sequence and one or more **other nucleotide sequences** which ensure transduction of a target neuronal cell by the retroviral vector and wherein the vector delivery system is from the group consisting of MLV, HIV and EIAV vectors. However, claims 23-24 recite that the **other nucleotide sequences** are from any lentivirus or any oncoretrovirus, which is broader than the MLV, HIV and EIAV vectors recited in claim 21.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David Guzo
November 16, 2003

PRIMARY EXAMINER